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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,328	04/08/2004	Roberto Takashi Sudo	32390-178943	9691

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,328	SUDO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03062002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating congestive heart failure, does not reasonably provide enablement for a method of treating a patient with a calcium sensitizer generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to calcium sensitizer provided in the specification. First, the instant claims cover disorders that are

known to exist and those that may be discovered in the future, for which there is no enablement provided. Test procedure and assay provided in the specification in pages 19-31, provide for example, test procedure for testing the activity of the compounds in congestive heart failure (see Example 4), however, there is nothing in the disclosure regarding how this test data correlates to generally treating a patient with or without the requirement of any specific treatment. The disorders encompassed by the instant claims include diverse types of disorders, e.g., cardiovascular disorders, systolic dysfunction, HIV infection, cancer, etc. (as can be seen from claim 15), some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

"Heart condition" includes several types of cardiovascular disorders, thromboses, etc. and therefore, embraces a vast array of problems, many of which are contradictory to others. Thus, the above term could include hypertension and hypotension and further, various types of arrhythmias; angina pectoris, the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischaemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol', arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine,

cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against all types of "heart conditions" generally.

Congestive heart failure is a progressive disorder that is frequently preceded by asymptomatic left ventricular systolic dysfunction. Endothelial dysfunction is a physiological dysfunction of normal biochemical processes carried out by endothelial cell, the cells that line the inner surface of all blood vessels, arteries and veins. Compromise of normal function of endothelial cells is characteristic of endothelial dysfunction. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces. Endothelial dysfunction can result from disease processes, as occurs in septic shock, as well as from environmental factors, such as from smoking tobacco products. A state of the art reference, Lerman (2002) provides that – "Although various interventions were shown to be associated with improvement of endothelial function, little is currently known about the clinical and prognostic impact of therapeutic improvement of endothelial function" (see http://www.nhlbi.nih.gov/meetings/workshops/wise/session02_lerman.pdf). Another reference, Koren (2002) indicates that "There are no specific published guidelines for the treatment of left ventricular diastolic dysfunction" (see http://www.dcmsonline.org/jax-medicine/2002journals/Feb2002/diastolic.htm).

The instant claim is directed to 'a method of treatment of HIV infection' (see claim 15), which is not sufficiently established in the specification that the instant compounds can treat HIV infection generally. The test data provided in the specification regarding the pharmaceutical activity of the compounds, to measure the toxicity, isometric tension in cardiac muscle, isolated

human skeletal muscle, etc. and there is insufficient evidence that these studies correlate anti-HIV activity. The obstacles to therapy of HIV are well documented in the literature, which include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus; and 2) the complexity and variation of the pathology of HIV infection in different individuals. HIV-specific immunity can control viral replication and delay disease progression but does not clear infection. Antiretroviral treatment consists of inhibitors that target for viral entry, reverse transcriptase, and viral protease. Therapy can control viral replication, restore immunity, and delay disease progression, but it cannot eliminate infection.

Marcus et al. (see the enclosed PubMed Abstract), in their recent publication expressed that 'despite advances, the global spread of HIV and especially its spread in developing countries continues almost unabated'. Also, van Heeswijk et al., (PubMed Abstract enclosed) stated that, "further clinical studies are needed to identify optimal combinations for treatment of antiretroviral naïve and experienced HIV-1 infected patients". Despite the unprecedented successes in the therapy of HIV infection, AIDS remains a major world health problem being the first cause of death in Africa and the fourth leading cause of death worldwide. Despite the success of protease and reverse transcriptase inhibitors, new drugs to suppress HIV-1 replication are still needed. Thus it is clear from the above evidence that the ability to treat diseases associated with HIV is highly unpredictable and has met with very little success.

The instant claims also include 'a method of treating cancer' (see claim 15). A 'cancer' (or tumor or proliferative disorder) is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization

and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The claims are further drawn to 'a method of treating a major injury', however, what the disclosure does not provide what type of "major injury" or type of injury to which organ or body part is intended by the recitation is not provided for. This term appears to cover any and all types of injuries known and those that are yet to be found. Further, the use of the compounds according to the specification includes treatment of inflammatory bowel diseases such as ulcerative colitis, which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual <http://www.merck.com/mrkshared/mmanual/section3/chapter31/31c.jsp>).

The therapeutic method of the instant claims includes treatment of inflammatory bowel

disease including Crohn's disease and ulcerative colitis, which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual). Bremner et al. (Expert Opin. Pharmacother. 2002) provide that "New therapies that affect immunomodulation offer the possibility of disease control in those unresponsive to conventional therapy and may reduce the need for further surgery. However, these treatments remain to be fully evaluated" (see page 820). Singh et al. (British Journal of Surgery, 2001) provide that 'the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood' (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that "Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective"; "All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders" (see page 90). This is indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the

unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, in the definition of R_2, the term "un-substituted phenol" does not find support in the specification, nor there are examples illustrating this structural feature. The specification provides -- unsubstituted phenyl -- as an option for R_2 and not "phenol" (see page 3, lines 1-2). Appropriate correction and/or clarification required.
2. In claim 9, the term "LASSBio-294" is not understood. As this term is not a recognized standard name, it is suggested that the term be replaced with the chemical name or the structural formula provided in page 9. The discrepancy is observed in claims 16 and 20.
3. Claim 23 provides a formula (III) having the variables R_1-R_8, however, no definitions are provided for any of the variables. An independent claim must contain all limitations within the claim or should be written in dependent on another claim containing the limitations.

Receipt is acknowledged of the Information Disclosure Statement filed on March 6, 2002 and a copy is enclosed herewith.

Allowable Subject Matter

Claims 1-8 and 16-23 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action. The references of record do not teach or fairly suggest the instantly claimed compounds.

Conclusion

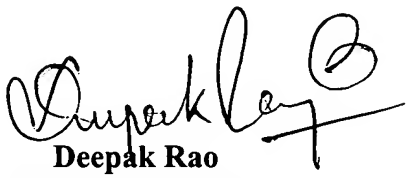
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

November 6, 2005